A new look at HDL in coronary disease: can we escape natural history?

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Heart

Can we escape natural history? A new look at HDL in coronary artery disease

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INTRODUCTION

In this issue, Seo et al, on behalf of all participants in the COACT (Catholic University of Koreaepercutaneous coronary intervention) registry, report that after placement of a drug-eluting stent in patients with coronary artery disease (CAD) and well controlled low-density lipoprotein (LDL-C) serum levels below 100 mg/dl, the high-density lipoprotein (HDL-C) serum concentrations remain a significant prognostic indicator of future cardiovascular events.1 The authors dichotomised the patient cohort according to HDL-C levels (40 mg/dl for men or 50 mg/dl for women) and compared major adverse cardiovascular event rates (MACE). Patients with low HDL-C levels (<40 mg/dl for men or <50 mg/dl for women) had a 40% higher rate of major adverse cardiac events (MACE), including all-cause death, non-fatal myocardial infarction and target vessel revascularisation (adjusted HR 1.404, 95% CI 1.111 to 1.774, p¼0.004). Their well conducted study confirms the results of a post-hoc analysis of the Treating to New Targets trial, in which a 39% lower risk for cardiovascular events was observed for patients with stable CAD in the highest versus lowest HDL-C quintiledeven under statin therapy and LDL-C levels <100 mg/dl.[2] In contrast to Treating to New Targets, however, Seo et al assessed the risk reduction in a postinterventional CAD cohort recruited for a national registry, thus reflecting a more 'real-world' scenario. However, there are also some caveats in a registry as compared to a prospective randomised trial: patients with low HDL-C were more likely to present with acute coronary syndrome (ACS), had a 10.3% higher prevalence of diabetes mellitus, and a 5.8% higher prevalence of arterial hypertension (see their table 1). To exclude that the higher event rate in the low HDL-C group was primarily driven by the higher prevalence of ACS and established risk factors, the authors used a propensity score matching to balance for clinical covariates. It is reassuring that the higher MACE rate and target vessel revascularisation associated with low HDL-C did not differ significantly between the total patient population and the propensitymatched population.

HDL AS A PROGNOSTIC INDICATOR

The prognostic relevance of high HDL-C plasma levels is well established in the medical literature. Since the 1980s when the Framingham study first demonstrated a reduced risk for coronary heart disease among subjects with HDL-C levels above the average range of 40e60 mg/dl,[3 4] several large cohort studies found HDL to be a strong independent predictor of lower CAD risk.[4-7] In consequence, both the ESC and

the US National Cholesterol Education Program recognised HDL as an independent risk marker and recommended screening for low HDL levels as part of primary and secondary prevention treatment.[8 9] An increase in HDL-C by 1 mg/dl is calculated to be associated with a 2% lower risk of CAD in men and a 3% lower risk in women.[2] Hence low HDL-C levels have become a new therapeutic targetdparticularly because of studies indicating that a reversal of the atherosclerotic disease process could be achieved by some interventions, increasing HDL-C levels [10 11] and enhancing the HDL-C mediated reverse cholesterol transport from the foam cells in the arterial wall to the liver (see Natarajan et al for a review[12]). It is well established that in the setting of high LDL-C levels, higher HDL levels are associated with protection from progression of atherosclerosis.[13] However, it is still unclear whether HDL-C retains its prognostic significance even under optimal control of LDL-C. In recent years, evidence is accumulating that even when there are very low LDL-C concentrations after intense lipid-lowering therapy in patients with coronary disease, lower HDL-C remains independently associated with increased cardiovascular risk.[2 14] The current study adds to this body of evidence.

HDL LEVELS AND FUNCTION

The simple strategy of pharmacologically increasing HDL-C concentration in the circulation may, however, not be a universal solution. Beyond pure quantity, HDL qualitydthat is, the functional properties of HDLdhave been shown to play a key role in the atheroprotective effects. HDL has been proposed to protect from atherosclerosis by promotion of macrophage cholesterol effluxdthat is, reverse cholesterol transportdbut also by stimulation of endothelial cell nitric oxide production and endothelial repair as well as anti-inflammatory and anti-oxidant effects.[15-17] However, these studies have largely been performed using reconstituted HDL or HDL isolated from healthy subjects. In the recent ILLUMINATE study, an increased rate of cardiovascular events was observed despite a substantial increase of the HDL cholesterol plasma levels in patients treated with torcetrapib in addition to standard statin therapy. This raises the question of whether HDL from patients with coronary disease retains vasoprotective properties.[18] Importantly, several recent studies have suggested that the vascular effects of HDL can be highly heterogeneous. A reduced macrophage cholesterol efflux capacity of apoB-depleted serum was associated with an increased risk of coronary disease in a caseecontrol study.[19] In several recent studies it was observed that

HDL from patients with coronary disease or diabetes, in contrast to HDL from healthy subjects, had lost the capacity to stimulate endothelial nitric oxide production, resulting in a loss of anti-inflammatory properties of the lipoprotein.[20-22] The molecular mechanisms underlying this 'HDL dysfunction' are still incompletely understood, but likely involve oxidative modification of the lipoprotein.[22] These studies therefore suggest that HDL-targeted therapies should not only increase HDL levels, but should also promote a vasoprotective on-treatment HDL in order to truly exert vasoprotective effects.

LIPID CONTROL AND/OR CORONARY INTERVENTION?

Interventional cardiologists are sometimes inclined to believe that the effective mechanical treatment of a high-grade coronary stenosis by implantation of a latest technology drug eluting stent solves the patient's problem. While the beneficial prognostic impact of percutaneous coronary interventions (PCI) is well established in ACS, it is highly debated among patients presenting with stable CAD. According to the COURAGE trial, optimal medical therapy may be an alternative strategy in stable CAD, with the same clinical outcome with respect to prognosis,[23] at least for patients that have clinical characteristics similar to patients randomised in the trial and who do not have extensive cardiac ischaemia. What COURAGE and several other studies focusing on optimal secondary prevention by use of b blockers, statins and platetelet inhibitors confirmed, is the paramount clinical importance of controlling cardiovascular risk factors. Even in ACS, an improved microcirculation immediately after PCI and a reduction in MACE achieved by aggressive LDL-C lowering has been reported.[24 25] It is still unclear whether an initial conservative strategy in patients with stable CAD and optimal medical therapy with LDL-C <70 mg/dl and pharmacological HDL-C increases >60 mg/dl may be superior to PCI plus usual care. The study by Seo et al indicates that targeting HDL post-PCI could further decrease adverse event rates. However, we are still lacking prospective randomised clinical studies in patients post-PCI on the additional benefit of pharmacologically increasing HDL-C. Until then we should follow the guidance of the recent position paper of the European Atherosclerosis Society Consensus Panel, which proposed that "therapeutic targeting of elevated triglycerides (≥1.7 mmol/l or 150 mg/dl), ... and/or low HDL-C (<1.0 mmol/l or 40 mg/dl) may provide further benefit. The first step should be lifestyle interventions together with consideration of compliance with pharmacotherapy and secondary causes of

dyslipidaemia. If inadequately corrected, adding niacin or a fibrate, or intensifying LDL-C lowering therapy may be considered."[26] In the study by Seo et al, the LDL-C target of LDL-C <70 mg was reached in 52.6% of all patients, which is more than in the last EUROASPIRE III study, where only 30.6% of patients on lipid-lowering medication achieved the target values for total cholesterol.[27] A recent study by Borden et al confirmed that less than half of the patients undergoing PCI in the USA receive optimal medical therapy before PCI, with little change after the publication of COURAGE.[28] One can only reiterate the authors' conclusion that "multidisciplinary teams could use ... this 'teachable moment' of an invasive procedure to impart to patients the importance of medication adherence, and engage the patient in a program that supports the transition of care so that important medications are implemented."[28] We are not lacking the evidence for effective risk control; the lack is in its clinical implementation. The study by Seo et al confirms that improved LDL-C control, and in the future, hopefully, HDL therapy, will result in improved outcomes for our patients.

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